DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Fiscal Year 2002 Budget Request

Witness appearing before the
Senate Subcommittee on Labor-HHS-Education Appropriations

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National Institute of Diabetes and Digestive and Kidney Diseases

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Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for FY 2002, a sum of $ 1,457,915,000, which reflects an increase of $ 154,098,000 over the comparable Fiscal Year 2001 appropriation. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) Of 1993. Prominent in the performance data is NIH's second annual performance report which compares our FY 2000 results to the goals in our FY 2000 performance plan. As performance trends on research outcomes emerge, the GPRA data will help NIH to identify strategies and objectives to continuously improve its programs.

The NIDDK supports research on a wide range of chronic, debilitating diseases including diabetes; hepatitis and other liver diseases; inflammatory bowel disease; interstitial cystitis and other bladder conditions; prostatitis and benign prostate enlargement; several anemias; and polycystic kidney disease and other causes of end-stage kidney failure. The economic burden of these diseases accounts for a major portion of U.S. health care expenditures. Advances in biomedical research are critical if we are to mitigate the human and economic burden of these diseases. With the generous support Congress has provided, NIDDK-supported scientists are well positioned to identify the causes of the diseases within our mission, to help identify people at risk for development of these diseases, and, ultimately, to provide novel approaches to prevention and treatment.

DIABETES

One of the most important health care issues facing our Nation is the increasing burden of diabetes. According to the Centers for Disease Control and Prevention (CDC), diabetes affects an estimated 16 million Americans, one-third of whom are unaware they have the disease and are therefore untreated. An estimated 30 million additional Americans have a pre-diabetic condition known as impaired glucose tolerance. Within the last year, scientists have made tremendous progress in

understanding and treating both type 1 and type 2 diabetes. Type 1, or juvenile diabetes, occurs when the body's immune system destroys the insulin-producing beta cells in the islets of the pancreas. Type 2 diabetes, previously called non-insulin dependent or adult-onset diabetes, results from the body's inability to respond to insulin effectively – a condition known as insulin resistance – followed by a failure of the beta cells to produce sufficient insulin.

People with type 1 diabetes must take regular insulin injections to survive. However, insulin represents only a treatment for type 1 diabetes, not a cure. Recent advances have created new hope for a cure for type 1 diabetes through pancreatic islet transplantation. The NIDDK is supporting several clinical trials to expand upon a promising study in which islet transplantation permitted a small number of people with type 1 diabetes to remain healthy for over a year without daily insulin injections. We are also supporting research on many aspects of beta cell development and function so that we can address the problem of the inadequate supplies of donor pancreatic tissue for transplantation, possibly by developing alternative sources of islet beta cells. In addition, we are supporting research on alternatives to lifelong immunosuppressive drug treatment currently required to prevent rejection of transplanted islets. One innovative approach uses a short course of therapy to teach the immune system to accept a transplant as "self," avoiding tissue rejection without global immunosuppression. Not only do these novel approaches to educating the immune system increase the likelihood of achieving a true cure for type 1 diabetes, they also offer hope of preventing the disease in those at risk. Trials of innovative prevention measures will be performed as part of our newly-created type 1 diabetes TrialNet.

Type 2 diabetes is a "complex genetic disease" with subtle changes in the function of several genes contributing to disease susceptibility. Despite the technical difficulties in identifying such gene changes, researchers studying a population of Mexican Americans who are particularly prone to type 2 diabetes identified changes in a gene –

NIDDM1 – that correlate with development of the disease. The product of this gene – calpain 10 – is present in pancreatic islets, muscle, and liver – all tissues that are involved in insulin and glucose processing. Scientists have identified at least three other chromosomal regions whose products may interact with NIDDM1 to increase susceptibility to type 2 diabetes. Knowledge of the genetic basis for diabetes susceptibility paves the way to improved prevention and diagnosis by identifying individuals at risk, and to improved treatment by providing new targets for therapy.

Obesity is a major risk factor for type 2 diabetes. The alarming increase in the number of people who are overweight or obese in the U.S. population has led to a coincident increase in type 2 diabetes in adults, and even in children and adolescents. Successful control of body weight could therefore profoundly diminish the incidence of type 2 diabetes. In just the past few years, there have been major advances in our understanding of how weight is regulated. Scientists have identified many of the steps in a complex pathway that controls both appetite and metabolic rate. An imbalance in this regulation can lead to the accumulation of excessive body fat. Until recently, the precise mechanism by which excess fat led to insulin resistance and type 2 diabetes was unclear. However, several recent advances have changed the way scientists view fat, and have underscored that fat – far from being an idle repository of excess energy – is in fact a dynamic tissue that produces a number of hormones with the potential to influence appetite and metabolism.

Leptin, a protein produced by fat cells that acts on the brain to suppress appetite, was discovered just six years ago, but has already entered clinical trials in humans. More recently, by "mining" mouse and human genome sequences, scientists have identified other hormones produced by fat cells that act on muscle and liver – the primary sites in the body of glucose metabolism and insulin action. For example, NIDDK grantees identified a protein produced by fat cells they termed "resistin," because it promotes insulin resistance. Obesity causes increased levels of resistin in

blood, thus providing a direct link between excess body weight and the diminished insulin sensitivity often seen in overweight individuals. Another group of NIDDK-supported investigators identified another protein produced by fat cells – called Acrp30 – that acts to increase fat metabolism in muscle, thereby promoting weight loss. Together, these studies indicate that fat cells produce hormones that may either promote or inhibit insulin responsiveness. Under normal circumstances, these two opposing signals keep each other in check. However, in obese individuals, this balance may be perturbed, and drugs that block or mimic these hormones may prove useful in both prevention and treatment of obesity and type 2 diabetes.

In addition to genetic susceptibility, the environment exerts an influence on the development of obesity and type 2 diabetes. The NIDDK is therefore supporting initiatives on environmental approaches to obesity prevention, including educational efforts. We are launching a major initiative aimed at prevention and treatment of type 2 diabetes in children and adolescents. A major multi-center clinical trial, the Diabetes Prevention Program (DPP), is testing the ability of lifestyle and drug intervention strategies to prevent type 2 diabetes in individuals with impaired glucose tolerance who are at high risk for the disease. The results of this trial, slated for completion in 2002, may have major public health implications for the prevention of type 2 diabetes.

Diabetes is the leading cause of end-stage kidney failure, new cases of blindness in adults, and non-traumatic lower limb amputations. It also causes increased susceptibility to urinary tract infections and a progressive form of fatty liver disease known as non-alcoholic steatohepatitis (NASH). Heart disease is the leading cause of death in diabetics, and the NIDDK is sponsoring a clinical trial – Look AHEAD – that will determine whether sustained weight loss in obese people with type 2 diabetes can reduce the incidence of cardiovascular complications. According to the American Diabetes Association, diabetes cost the country $98 billion in 1997, and over half of this expense was related to the disability, lost productivity, and early mortality associated

with the disease. We know that prevention of diabetes, and where prevention is not possible, optimal management of the disease, not only alleviates human suffering but is cost-effective. For this reason, the NIDDK is exploring many avenues of prevention and treatment for diabetes and its complications, including basic genetic and molecular studies, development of animal models to facilitate testing of new drugs, therapeutic gene transfer techniques, and drug intervention trials. We are also increasing the resources available to our Diabetes Research and Training Centers to enhance efforts in diabetes prevention and treatment, and are expanding the National Diabetes Education Program (NDEP), which supports community-based multi-cultural efforts to increase diabetes awareness, to improve care of people with diabetes.

HEPATITIS C AND OTHER CHRONIC LIVER DISEASES

The NIDDK supports research on many other serious diseases, including liver disease arising from a range of causes. In the U.S., infection with the hepatitis C virus is a leading cause of liver failure and can lead to liver cancer. The newly-initiated HALT-C trial is testing whether long-term antiviral treatment can eliminate the hepatitis C virus in patients who fail to respond to conventional treatment. We are also initiating a trial of interferon treatment for hepatitis C in African Americans, whose disease is often resistant to the standard treatment regimen.

The NIDDK is also studying NASH, a disease characterized by fat deposition in the liver that can lead to inflammation, fibrosis, and cirrhosis. NASH is most often seen in overweight individuals and is associated with diabetes and insulin resistance. NIDDK plans a clinical research network to study the natural history, complications, and possible therapies for NASH. Whatever the precipitating cause, liver failure is ultimately only treatable currently through liver transplantation. Unfortunately, the need for donor livers far outstrips the supply of available organs. The NIDDK organized a workshop in December 2000 to assess recent advances in adult-to-adult living donor liver transplantation. An important outcome of this meeting is the development of a research initiative for a prospective database to further knowledge about the

consequences of living donor liver transplantation, both for the donor and the recipient.

INFLAMMATORY BOWEL DISEASE AND OTHER DIGESTIVE DISEASES

The NIDDK sponsors studies on the inflammatory bowel diseases (IBDs), ulcerative colitis and Crohn's disease, including efforts to identify their genetic and environmental causes. A contributing factor to both conditions is believed to be an inappropriate reaction by the body's immune system to the bacterial flora normally present in the gut. Previous research on mouse models of IBD led to the discovery of a factor responsible for gut inflammation, and ultimately to development of an antibody to neutralize this factor that has been shown to be effective in treatment of Crohn's disease. In recent studies, NIDDK-supported investigators have identified a strain of mice that spontaneously develop intestinal inflammation remarkably similar to Crohn's disease. They have shown that these mice can be efficiently used to test new treatments for the disease. In the future, the NIDDK plans an IBD Genetics Consortium to facilitate identification of susceptibility genes, and a clinical network to accelerate studies of prevention and treatment of IBD.

END-STAGE RENAL DISEASE AND POLYCYSTIC KIDNEY DISEASE

According to the United States Renal Data System, individuals with diabetes account for approximately 45 percent of patients with end-stage kidney disease. Because of this, the NIDDK is concentrating its efforts on preventing diabetic kidney disease and slowing its progression. The Institute is expanding the FIND (Family Investigation of Nephropathy and Diabetes) consortium to identify genetic loci and, ultimately, the specific genes that influence susceptibility to, and severity of, diabetic nephropathy. The Institute is also investigating the causes and possible new treatments for FSGS (Focal Segmental Glomerular Sclerosis), an important cause of kidney failure in children and young adults. The Institute plans a multi-center clinical trial to study treatment approaches for FSGS.

NIDDK support is also making a difference in understanding other important causes of irreversible kidney failure such as polycystic kidney disease (PKD). NIDDK-funded researchers are studying non-invasive means of assessing PKD progression, which will facilitate a planned clinical trial of drug intervention to slow progression. A new prospective observational study is aimed at understanding the factors responsible for the high incidence of heart disease in patients with end-stage kidney disease. Because folate lowers levels of homocysteine, a known risk factor for heart disease, we are also planning a clinical trial on the use of high doses of this vitamin in the prevention of heart disease in renal transplant recipients. We are also launching a National Kidney Disease Education Program to address the rising incidence of end-stage kidney disease, particularly in various minority groups.

UROLOGIC DISEASES

The NIDDK is sponsoring initiatives to promote understanding of a range of urologic diseases, including interstitial cystitis, benign prostatic hyperplasia (BPH), and chronic prostatitis. The Institute is working to organize a compendium of "Urologic Diseases in America" that will describe the changes in the epidemiology, health economic impact, and practice patterns for each of the diseases currently included within the scope of urology. The Institute has recently organized a Progress Review Group for Bladder Research to develop a future research agenda. We are also building on our Medical Therapy of Prostatic Symptoms (MTOPS) Trial with a national registry of prostate tissue samples that will allow urology investigators to harness genomic technology to study BPH and prostate cancer.

The NIDDK continues to pursue many approaches to combat the serious diseases within its mission in order to relieve the burden they place on individuals, families, and the Nation. I appreciate the opportunity to address the Committee, and I thank you for your attention. I look forward to answering any questions you might have.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Biographical Sketch

NAME	Allen M. Spiegel, M.D.
POSITION	Director, National Institute of Diabetes and Digestive and Kidney Diseases
BIRTHPLACE	Germany
DATE	May 18, 1946
EDUCATION	B.A., Columbia College, 1967
	M.D., Harvard Medical School, 1971
EXPERIENCE	
1999-present	Director, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
1990-1999	Director, Division of Intramural Research, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
1993-present	Chief, Metabolic Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
1988-1993	Chief, Molecular Pathophysiology Branch, Metabolic Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
1985-1988	Chief, Section on Molecular Pathophysiology, Metabolic Diseases Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, NIH
1977-1984	Senior Investigator, Metabolic Diseases Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, NIH
1973-1976	Fellow, NIH Endocrinology Training Program, Clinical Associate, Metabolic Diseases Branch (Dr. G. D. Aurbach,

	Chief), National Institute of Arthritis, Metabolism, and Digestive Diseases, NIH
1971-1973	Intern and Assistant Resident in Medicine, Massachusetts General Hospital, (Dr. Alexander Leaf, Chief)

HONORS AND AWARDS

1966	Elected to Phi Beta Kappa
1967	B.A. Summa Cum Laude
1971	Elected to Alpha Omega Alpha
1971	M.D. Cum Laude
1988	Outstanding Service Medal – U.S. Public Health Service
1990	Meritorious Service Medal – U.S. Public Health Service
1990	Jacobaeus Prize – Nordisk Insulin Foundation
1993	Plenary Lecturer – Japan Endocrine Society
1993	Aurbach Memorial Lecturer – American Society for Bone and Mineral Research
1994	Harrison Memorial Lecturer – Endocrine Society of Australia
1996	Komrower Memorial Lecturer – Society for the Study of Inborn Errors of Metabolism
1998	Edwin B. Astwood Lecture Award – Endocrine Society (U.S.A.)

PROFESSIONAL ORGANIZATIONS

American Federation for Clinical Research

The Endocrine Society

American Society for Bone and Mineral Research

American Society for Clinical Investigation

American Society for Biochemistry and Molecular Biology

Association of American Physicians

LICENSURE AND CERTIFICATION:

Diplomate American Board of Internal Medicine, 1974

Board Certified in Endocrinology, 1975

Licensed in Medicine, Maryland